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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,879	07/25/2003	Jang Han	072121-0189-Reg	1049

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NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY- X100B
P.O. BOX 8097
Emeryville, CA 94662-8097

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
02/25/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,879	HAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,14,15,17-20,24,25,43,45-56,67-74,81,84,87 and 89-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,14,15,17-20,24,25,43,45-56,67-74,81,84,87 and 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment data*.

DETAILED ACTION

This Office action is in response to the communication filed 11-16-10.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-16-10 has been entered.

Response to Arguments and Amendments

Applicant's arguments with respect to claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al (USPN 6,107,027), Draper et al (USPN 5,610,054), and Jadhav et al (US 2005/0209180), the combination in view of Anderson et al (USPN 6,174,868) , Fire et al (USPN 6,506,559), the combination further in view of Fosnaugh et al (US 2003/0143732), Morrissey et al (US 2003/0206887) and McKay et al (USPN 6,133,246), and Alsobrook et al (US 2003/0219823).

The claims are drawn to compositions and methods of making a modified siRNA, methods of inactivating, inhibiting and/or treating hepatitis C virus (HCV) comprising administration of siRNA sharing at least 95% to 99% identity with SEQ ID NOs. 14-27, which target and inhibit nucleic acids encoding HCV, and which siRNA further comprise 2'-fluoro or 2'-O-methyl modified groups, a modified cytosine, which siRNA are optionally expressed via an expression vector, and which siRNA are operatively linked to a first and second promoter, comprising a U6 and H1 promoter, and which siRNA optionally further comprise modified internucleotide linkages.

Kay et al (USPN 6,107,027) teach methods of inactivating HCV comprising administration of antisense oligonucleotides that share complete identity with

nucleotides 1-16 of SEQ ID NO. 15 (see SEQ ID NO: 6 of Kay and its alignment with the instantly claimed SEQ ID No. 15).

Draper et al (USPN 5,610,054) teach methods of inactivating HCV comprising administration of ribozymes comprising antisense oligonucleotides that share complete identity with nucleotides 1-23 of SEQ ID NO. 15, and the incorporation of 2'-O-methyl residues for enhancing oligonucleotide stability (see SEQ ID NOs: 43, 44, 45 and their alignment with the instantly claimed SEQ ID No. 15; see section entitled "Ribozyme Stability").

Jadhav et al (US 2005/0209180) teach methods of inactivating HCV comprising administration of an siRNA which shares complete identity with nucleotides 2-20 of SEQ ID NO. 15, and the incorporation of 2'O-methyl, 2'-Fluoro, modified pyrimidines including cytosine residues for enhancing oligonucleotide stability, target binding and cellular uptake (see SEQ ID NO: 816 and its alignment with the instantly claimed SEQ ID No. 15; see also paragraphs 0038-0128, claims 16-18).

The primary references do not teach an siRNA molecule which comprises 23 nucleotides and which shares 95-99% with SEQ ID NO. 15 and includes all of the modifications instantly claimed, nor the use of U6 and H1 promoters to drive expression of siRNA in an appropriate expression vector.

Anderson et al (USPN 6,174,868) teach the inhibition of HCV RNA translation comprising the administration of an antisense oligonucleotide that specifically targets nucleic acids encoding HCV, and which antisense share 100% identity with the target HCV gene, which antisense optionally further comprises modified phosphate

internucleotide linkages, modified cytosines, and/or 2'-O modified sugar residues (see entire document).

Fire et al (USPN 6,506,559) teach the use of inhibitory oligonucleotides in inhibiting the expression of target genes in vitro and in vivo. Fire teaches the advantages of using siRNA for target gene inhibition compared to other inhibitory oligonucleotides, including antisense and ribozymes, and teaches the use of expression vectors for expressing siRNA molecules in an organism. Fire also teaches the incorporation of modified internucleotide linkages and modified nucleotides into siRNA molecules for enhancing oligonucleotide stability, target binding and cellular uptake (see the abstract; col. 1-5, 7; claims 1-6, 10, 21).

Alsobrook et al (US 2003/0219823) teach expression vectors comprising U6 or H1 for expression of siRNA in an appropriate target cell (see esp. paragraph 0090).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh et al also teach compositions comprising modified and

unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'- modifications on siRNA, including 2'-fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

McKay et al (USPN 6,133,246) teach numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases including modified cytosines, modified internucleotide linkages, 2'-β-D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

It would have been obvious to design and utilize siRNA molecules that share at least 95-99% identity with SEQ ID NO. 15 for inhibiting HCV replication and HCV infection because antisense and other inhibitory oligonucleotides, including antisense, ribozymes and siRNA, comprising sequence identity with this well known HCV target region were well known in the art at the time the instant invention was made, as illustrated by the teachings of Kay, Draper, and Jadhav, and siRNA molecules were well

known in the art to target and inhibit a target gene of known sequence more efficiently than antisense or ribozymes, as taught previously by Fire. One would have been motivated to utilize siRNA molecules comprising SEQ ID No. 15 because this target region of the HCV sequence was well known to be accessible to antisense, siRNA and ribozyme oligonucleotides, and siRNA were known to be more effective inhibitors of target gene expression.

One would have been motivated to inhibit the expression or replication of HCV because HCV infections are known to cause deleterious effects in humans, as taught previously by many in the art, including by not limited to Anderson. One of ordinary skill would have reasonably expected to utilize the inhibitory oligonucleotides, previously taught and tested by Draper, Kay and Jadhav, in siRNA constructs and achieve target gene inhibition because of the known advantages of siRNA, as taught previously by Fire et al, and the accessibility of this target region of HCV was also well known in the art, as previously disclosed by Kay, Jadhave and Draper.

One of ordinary skill in the art would have been motivated to express siRNA molecules, either as a single, self-complementary molecule, or as two separate strands, because expression of siRNA within a cell from an appropriate expression vector provides increased siRNA within a target cell. One of ordinary skill in the art would have been motivated to use the well known and reliable U6 and H1 promoters to drive expression in an appropriate expression vector because these promoters are well known in the art to provide for predictable and high expression of siRNA in a target cell, as taught previously by AlsoBrook et al.

It would have been obvious to incorporate 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise modified nucleobases, including modified cytosines into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Draper, Jadhav, Fosnaugh, Morrissey, Anderson, Fire and McKay all teach the advantages of incorporating these modifications into inhibitory oligonucleotides for enhancing target gene binding, cellular uptake and oligonucleotide stability. One of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation, and one of ordinary skill in the art would have expected that the siRNA molecules, modified as instantly claimed, would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA. One of ordinary skill in the art would have reasonably expected that these modifications would provide for the advantages previously taught, of enhancing target binding and oligonucleotide stability, and would lead to improved target gene inhibition.

For these reasons in the instant invention would have been obvious to one of skill at the time of filing.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** The examiner's office hours are generally Monday-Friday, 10:30am - 7pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita, can be reached on (571) 272-2876. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-22-11

/Jane Zara/

Primary Examiner, Art Unit 1635